

I claim:

1. A drug discovery method for identifying a compound that modulates the induction of PSD-95 by the Nrg-1/Eos signaling pathway comprising :

(i) contacting one or more test compounds with Nrg-ICD or a portion thereof, wherein the Nrg-ICD or portion thereof is encoded by a nucleic acid that hybridizes to a nucleic acid having SEQ ID NO: 1 in 5.times.SSC at 42.degree. C.; and (ii) identifying the binding between the one or more test compounds and Nrg-ICD or a portion thereof.

2. The method of claim 1, further comprising the step of exposing a cell to an identified compound from step (ii) and determining whether the identified compound modulates translocation of Nrg-ICD into the nucleus of the cell.

3. The method of claim 2, wherein modulation of translocation is measured fluorometrically.

4. The method of claim 1, further comprising the step of exposing a cell to an identified compound from step (ii) and determining whether the identified compound binds to Eos.

5. A drug discovery method for identifying a compound that modulates binding of Nrg-ICD with a binding site of Eos, comprising:

(i) contacting one or more test compounds with Nrg-ICD or a portion thereof and with at least one binding site of Eos, wherein the Nrg-ICD is encoded by a nucleic acid that hybridizes to a nucleic acid having SEQ ID NO: 1 in 5.times.SSC at 42.degree. C.;

(ii) contacting Nrg-ICD or a portion thereof with the at least one binding site of Eos in the absence of the one or more test compounds; and

(iii) identifying a difference in binding between Nrg-ICD or a portion thereof and with the at least one binding site of Eos between the contacting of (i) and the contacting of (ii).

6. The method of claim 5, wherein step (i) occurs after step (ii) by adding the one or more test compounds to a solution prepared in step (ii).

7. A drug discovery method for identifying a compound that modulates translocation of Nrg-ICD into a cell nucleus, comprising:

(i) contacting a cell with one or more test compounds; and

(ii) detecting movement of Nrg-ICD from the cell cytoplasm into the cell nucleus.

8. The method of claim 7, wherein movement of Nrg-ICD is indirectly detected by measuring the amount of Nrg-ICD in the cell nucleus after step (i).

9. The method of claim 7, wherein detection is carried out fluorometrically.
10. The method of claim 7, wherein the Nrg-ICD is produced transgenically within the cell.
11. The method of claim 9, wherein the Nrg-ICD comprises a conjugate of a polypeptide encoded by a sequence that is at least 90% homologous with SEQ ID NO: 1 and a detectable label.
12. The method of claim 9, wherein the Nrg-ICD comprises a conjugate of a polypeptide encoded by a sequence that is at least 95% homologous with SEQ ID NO: 1 and a detectable label.
13. A method for identifying a compound which promotes or inhibits translocation of Nrg-ICD across the nuclear membrane of a cell, comprising:
 - (i) transgenically expressing in cells, a polypeptide complex comprising a nuclear localization sequence of Nrg-ICD and a detectable label, wherein the localization sequence of Nrg-ICD is at least 90% homogeneous with a portion that exceeds 20 amino acids of SEQ ID NO: 1; and
 - (ii) contacting the cells with test compounds and determining whether a test compound affects translocation of Nrg-ICD across the nuclear membrane of the cell.
14. The method of claim 13, wherein the nuclear localization sequence is selected from the group consisting of SEQ ID NO: 3 [KTKKQRKK] and SEQ ID NO: 4 [PRLREKK].
15. The method of claim 13, wherein the cells are neurons.
16. The method of claim 13, wherein the detectable label is selected from the group consisting of green fluorescent protein, a chemilumiphore, an antigenic peptide sequence and a regulatory marker.
17. A method for identifying a compound that promotes or inhibits translocation of Nrg-ICD across the nuclear membrane of a cell, comprising:
 - (i) transgenically expressing in cells, a polypeptide complex comprising a nuclear localization sequence of Nrg-ICD and a regulatory marker, wherein the localization sequence of Nrg-ICD is at least 90% homogeneous with a portion that exceeds 20 amino acids of SEQ ID NO: 2 and the regulatory marker influences the expression of a gene when present within the nucleus of the cell; and

(ii) contacting the cells with test compounds and determining whether a test compound affects translocation of Nrg-ICD across the nuclear membrane of the cell.

18. The method of claim 17, wherein the regulatory marker is selected from the group consisting of a promoter and an enhancer.

19. The method of claim 17, wherein the cell nucleus comprises a foreign gene that produces a protein that conveys a selectable trait to the cell and the regulatory marker is a promoter or enhancer of that foreign gene.

20. A method for identifying a compound that modulates the proteolysis of Neu-1 to form Nrg-ICD, comprising:

- (i) incubating a cellular membrane form of Neu-1 in the presence of the compound; and
- (ii) detecting the formation of a carboxylic end portion of Neu-1 that is less than 60 kilodaltons in size.

21. The method of claim 20, wherein the cellular membrane form of Neu-1 is intact cells.

22. The method of claim 20, wherein the carboxylic end portion of Neu-1 is approximately 35 kilodaltons in size.

23. The method of claim 20, wherein detection of the carboxylic end portion comprises detection of an immunologically reactive water soluble polypeptide.

24. A method for identifying a compound that modulates gene activity by binding to an Ikaous 1/2 sequence, comprising:

- (i) providing transgenic cells that contain a reporter gene operably coupled to a promoter that comprises Ikaous 1/2 sequence;
- (ii) contacting the cells with one or more test substances; and
- (iii) detecting the induction of the reporter gene in response to one or more test substances.

25. The method of claim 24, wherein the cells transgenically express Neu-1.

26. A fusion polypeptide of a pharmaceutically active compound discovered by the method of any of claims 1 through 22, comprising a first polypeptide portion of between 8 and 50 amino acids long that exhibits binding to Nrg-ICD or Eos and a second polypeptide portion comprising a transporter moiety of between 10 and 20 amino acids long.

27. The fusion compound of claim 26, wherein the second polypeptide portion has a sequence that is selected from the group consisting of SEQ ID NO:4 [YGRKKRRQRRR] and SEQ ID NO: 5 [RQIKIWFQNRRMKWKK].

28. The fusion polypeptide of claim 26, wherein the pharmaceutically active compound binds Neu-1

29. A method for enhancing learning in an animal, comprising providing to the animal a compound that modulates the formation or translocation of Nrg-ICD into the nucleus of a nerve cell, wherein the compound is a fusion compound as described in claim 26.

30. A method for preventing neuronal excitotoxicity in an animal, comprising providing to the animal a pharmaceutical that attenuates the nuclear signaling pathway of Neu-1

31. A transgenic animal with enhanced learning capability, produced by the process of stably incorporating an exogenous Neu-1 gene into the animal and expressing the gene .

32. The transgenic animal of claim 31, wherein the added gene is expressed constitutively in nerve cells.

33. An isolated protein complex, comprising primarily of Ng-ICD and Eos.

34. A vector that comprises a gene encoding Nrg-ICD and a gene encoding Eos.